CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	215256
Supporting document/s:	1
Applicant's letter date:	12/04/2020
CDER stamp date:	12/14/2020
Product:	Semaglutide injection
Indication:	Adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management [redacted] (b) (4) [redacted] (b) (4) in adult patients with obesity or excess weight in the presence of at least one weight-related comorbid condition
Applicant:	Novo Nordisk Inc
Review Division:	Division of Diabetes, Lipid Disorders, and Obesity
Reviewer:	Elena Braithwaite
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Semaglutide is a glucagon-like peptide-1 (GLP-1) analog for once-weekly subcutaneous administration. It is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. This application is a 505(b)(1) NDA and the applicant is seeking approval for semaglutide as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management in adult patients with obesity or excess weight in the presence of at least one weight-related comorbid condition.

1.2 Brief Discussion of Nonclinical Findings

No new toxicology studies were submitted to support the weight management indication, as a standard nonclinical program was conducted and reviewed under the diabetic indication (IND 79754 and NDA 209637). Two additional pharmacology studies to investigate the mechanism of semaglutide-induced body weight loss were submitted for the weight management indication and are reviewed in this document. The labeling was revised to account for the higher dose proposed for the weight management indication (2.4 mg/week as compared to 1 mg/week for the diabetes indication).

<u>Pharmacology</u>
Semaglutide selectively binds to and activates the human GLP-1 receptor (GLP-1R), which is expressed in peripheral tissue as well as several areas of the brain. After repeated subcutaneous administration of semaglutide in mice, fluorescently tagged semaglutide distributed to several areas of the brain that are involved in food regulation. Semaglutide distributed to regions that are both protected (hypothalamus including the arcuate hypothalamic nucleus and septum) and not protected (circumventricular organs meninges and choroid plexus) by the blood brain barrier. Additionally, a single subcutaneous administration of semaglutide (0.1 mg/kg) in mice resulted in increased neuronal activation, as determined by c-Fos expression (an immediate early gene that is induced after GLP-1R activation), in several brain areas.

<u>Safety Pharmacology</u>
Treatment-related effects on the CNS (abnormal gait, decreased touch response, passivity, increased urination, dirty muzzle, lethargy and piloerection) and urinary system (increases in urine volume and sodium, potassium, and chloride concentrations) were noted in rats up to 8 hour post-dose at the clinical exposure. Semaglutide did not adversely affect the cardiovascular system in vitro and there were no ECG changes in monkeys following single doses. However, in a pivotal 52-week repeat dose toxicology study in monkeys, a chronic left bundle-branch-block occurred in one high-dose female at an exposure 5-fold above the MRHD, based on AUC. There were no adverse effects on respiratory function in rats.

<u>Absorption, Distribution, Metabolism and Excretion</u>

Semaglutide was well absorbed from the subcutaneous injection site, with a bioavailability of 86% in monkeys and was highly bound to plasma proteins (>99%) with albumin shown to be the primary binding site. Mean terminal half-lives were 7.5 h (mouse), 12 h (rat), 54 h (monkey) and 149 h (human). After subcutaneous administration, semaglutide exposure increased linearly in a dose-proportional manner, was comparable between sexes, and showed slight accumulation (1.5- to 5-fold) over time across species. In the monkey, the volume of distribution was 0.2 L/kg which corresponds to the volume of extracellular water, indicating that semaglutide distributes to plasma and peripheral tissues to the same extent as albumin. Semaglutide was absorbed and secreted in the milk after a single subcutaneous administration in rats at day 10 post-partum. Semaglutide levels in milk were 3 to 12-fold lower than in maternal plasma.

In rats, semaglutide was detected in all tissues (with the exception of the lens of the eye) after subcutaneous administration. Distribution to the brain and spinal cord was low; but, higher levels of semaglutide-related radioactivity were observed in the choroid plexus, meninges and pineal body after a single subcutaneous injection.

Semaglutide is metabolized by degradation of the peptide backbone and the fatty octadecanedioic acid before being eliminated predominately in the urine and feces.

General Toxicity

The toxicity profile of semaglutide was evaluated in mice, rats, and monkeys for up to 3, 6, and 12 months in duration, respectively. After mice were subcutaneously administered semaglutide for 13 weeks, the primary histopathological microscopic finding was focal C-cell hyperplasia and C-cell nests in the thyroid, and dilated ultimobranchial ducts in all semaglutide-treated groups (6-fold the MRHD based on AUC). In the liver, decreased absolute and relative liver weights correlated with decreased liver glycogen content; however, these findings are considered secondary to the pharmacodynamic activity of semaglutide. Lobar necrosis in one male and minimal centrilobular hypertrophy of the liver were observed in some of the male mice (64-fold MRHD). A NOAEL could not be established.

Rats subcutaneously administered semaglutide for a duration of at least 26-weeks experienced reversible, minimal Brunner's gland hypertrophy (non-adverse). The NOAEL for this study was the highest dose examined (0.6 mg/kg/day, 10-fold the MRHD).

In the 12-month study in monkeys, a bigeminal rhythm with two episodes of sinus tachycardia in Week 13 and a continuous left bundle branch block-like recording that persisted from Week 26 to Week 52 was observed in one high dose female at 5-fold the MRHD. Additionally, slight multifocal myocardial vacuolation and degeneration, with karyomegaly, in the left ventricle were observed in one high-dose male at 10 to 12-fold the MRHD. A relationship to treatment could not be excluded. The NOAEL was 0.06 mg/kg, 2-fold the MRHD based on AUC.

Reproductive Toxicity

Reproductive and developmental toxicity of semaglutide has been assessed in rats, rabbits and monkeys. In the pivotal combined fertility and embryo-fetal toxicity study in rats, pharmacologically-mediated, dose-dependent decreases in maternal body weight gain and major fetal malformations [cardiovascular abnormalities (retro-esophageal aortic arch, double aortic arch, and membranous ventricular septal defect) and short tibia (malrotated hindlimb)] were observed at the clinical exposure. Mechanistic studies showed that semaglutide caused embryotoxicity in rats through GLP-1 receptor-mediated impairment of inverted yolk sac function. However, involvement of additional mechanisms leading to embryotoxicity in rats cannot be completely excluded. No effects were observed on male fertility.

In an embryo-fetal toxicity study conducted in rabbits, body weight loss was observed throughout GD 11-14 at the clinical exposure. There was also a trend for a slight increase in post-implantation loss due to early resorptions, which resulted in slightly lower mean litter sizes and weights. Minor skeletal abnormalities (additional sternebral centers, bridge of ossification/partially fused/fused sternebra, unossified/incompletely ossified metacarpals/phalanges) and minor visceral abnormalities (dilated renal pelvis, additional liver lobe, and forepaw flexure) were observed at the clinical exposure.

Embryo-fetal development was also investigated in the cynomolgus monkey. Monkeys given a bolus subcutaneous dose of semaglutide on GDs 16, 18 and 20 and every third day thereafter until GD 50 experienced decreased maternal body weight during the dosing phase at all doses examined. A few sporadic abnormalities (focal reddening of the skin, kinked and stiff wrist, blood accumulation under the skull causing misshapen right brain hemisphere, fused kidneys, liver cysts and shift in alignment of the vertebrae, ribs, and first sternebra, at the cervico-thoracic border) were observed in fetuses at ≥2-fold the MRHD. Because these findings exceeded the concurrent control values and the historical control range, a relationship to treatment could not be excluded.

Pre- and postnatal development was evaluated in the monkey. Monkeys were subcutaneously administered semaglutide on GD 16, 18, 20, and every third day thereafter until GD 140. Maternal weight loss was observed in all treated groups until GD 50 at the clinical exposure and was associated with an increased incidence of early pregnancy loss at 3-fold the MRHD. Lower infant body weights at birth were also observed; but, by Day 91, body weights were similar across all groups. Semaglutide treatment did not result in neurobehavioral impairment.

Juvenile Animal Study

In juvenile rats, administration of semaglutide resulted in reduced food consumption, body weight gain, and delayed sexual maturation in all treated groups at the clinical exposure. However, semaglutide exposure did not have an adverse impact on estrous cyclicity, mating performance or fertility.

Genetic Toxicity

Semaglutide tested negatively for genotoxicity in a standard battery of tests (Ames test, in vitro human peripheral blood lymphocyte chromosome aberration test, and in vivo micronucleus test in bone marrow from treated rats).

Carcinogenicity
In a 2-year carcinogenicity study in CD-1 mice, a statistically significant increase in the incidence of thyroid C-cell adenomas and combined C-cell adenomas and carcinoma was observed in males (pairwise comparison) and females (trend and pairwise tests) at all dose levels (≥0.6-fold the MRHD).

In a 2-year carcinogenicity study in Sprague Dawley rats, a statistically significant increase (pairwise comparison) in thyroid C-cell adenomas was observed in males and females at all dose levels, and a dose-dependent and statistically significant increase (pairwise comparison) in thyroid C-cell carcinomas was observed in males at doses > 0.01 mg/kg/day (2-fold the MRHD).

1.3 Recommendations

1.3.1 Approvability

The nonclinical data support market approval of subcutaneously administered semaglutide as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management in adult patients with obesity or excess weight.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
RN910463-68-2

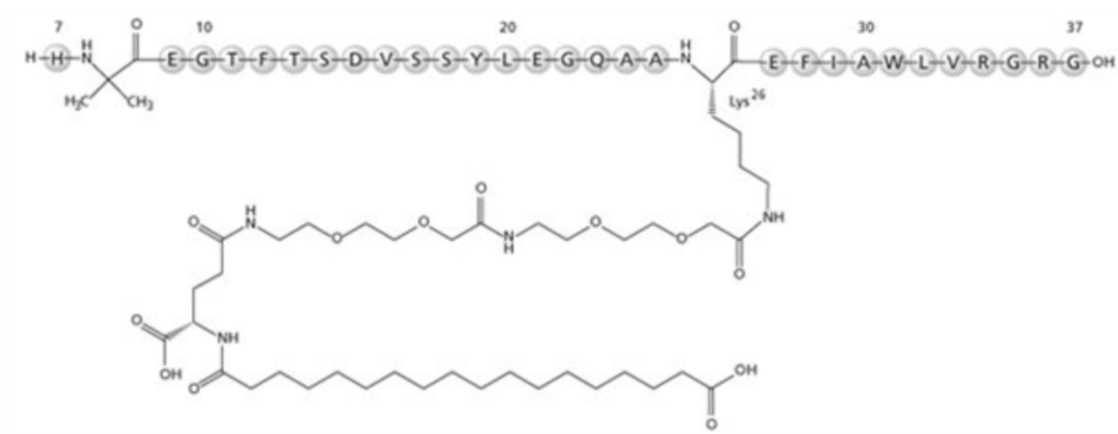
Generic Name
Ozempic

Code Name
Semaglutide, NNC0113-0217

Chemical Name
Nε26[(S)-(22,40- dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa- 9,18,23-triazatetracontan-1-oyl)] [Aib8, Arg34] GLP-1-(7-37) peptide

Molecular Formula/Molecular Weight
$C_{187}H_{291}N_{45}O_{59}$/4113.58 g/mol

Structure or Biochemical Description
Semaglutide has been engineered to have a low clearance and thereby a long elimination half-life. The extended half-life is achieved by albumin binding facilitated by a fatty di-acid attached to the peptide backbone through a hydrophilic linker at lysine in position 26. In addition, the peptide backbone has been modified in position 8 (alanine to 2-aminoisobutyric acid) in order to reduce degradation by the DPP-4 enzyme.



Pharmacologic Class
Long acting glucagon-like peptide-1 (GLP-1) receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

<u>Semaglutide (subcutaneous injection)</u>
IND 79754, Type 2 Diabetes Mellitus
IND 126360, Chronic weight management

(b) (4)

(b) (4) [redacted]

NDA 209637, adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Semaglutide (oral)

(b) (4) [redacted]

NDA 213051, tablet, an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

2.3 Drug Formulation

Semaglutide drug products are filled in a 1 ml pre-fillable syringe and subsequently assembled in a single dose pen-injector.

Table 1: Composition of semaglutide drug products

Compound	Quantity per ml	Function	Reference to standard
Active substance			
Semaglutide	0.5 mg 1.0 mg 2.0 mg 2.27 mg 3.2 mg	Drug substance	Novo Nordisk A/S
Excipients			
Disodium phosphate, dihydrate	1.42 mg	(b) (4) [redacted]	USP, Ph. Eur.
Sodium chloride	8.25 mg	[redacted]	USP, JP, Ph. Eur.
Hydrochloric acid	q.s[a]	pH adjustment	USP, JP, Ph. Eur.
Sodium hydroxide	q.s[a]	pH adjustment	USP, JP, Ph. Eur.
Water for injections	[redacted]	(b) (4) [redacted]	USP, JP, Ph. Eur.

[a] To reach pH 7.4

Table copied from the Applicant's submission (Table 1, 3.2.P.1.)

2.4 Comments on Novel Excipients

There are no novel excipients in the drug formulation. All excipients have been used previously in FDA-approved products for subcutaneous use at levels equal to or higher than those present in the formulation.

2.5 Comments on Impurities/Degradants of Concern

All impurities/degradants present in the drug product are considered to be reasonably safe.

(b) (4)

[redacted]

(b) (4)

Table 2: Safety evaluation of leachables observed in long term leachables study

Compound	Exposure / threshold limit		Maximum calculated patient exposure[a]	Margin of exposure to PDE, QT, AI or pRBC
	Type	Limit		

(b) (4) [redacted]

Table copied from the Applicant's submission (Table 2).

2.6 Proposed Clinical Population and Dosing Regimen

Semaglutide is proposed to be used as an adjunct to a reduced calorie meal and increased physical activity for chronic weight management (b) (4) [redacted] in adult patients with an initial body mass index of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (excess weight) in the presence of at least one weight-related comorbid condition. To minimize gastrointestinal symptoms, a dose escalation regimen will be employed (0.25, 0.5, 1.0, and 1.7 mg/week) with dose increases every four weeks until a therapeutic and/or maintenance dose of 2.4 mg/week is achieved. Women must discontinue use at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

2.7 Regulatory Background

Semaglutide for subcutaneous injection was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in 2017 (NDA 209637). In 2020, a supplement was approved for semaglutide to be used to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

All pivotal studies submitted under IND 79754 were cross referenced to support the development of semaglutide for the chronic weight management indication (IND 126360).

3 Studies Submitted

3.1 Studies Reviewed

Study No.: 321410	Semaglutide: Neuronal activation in mouse brain following semaglutide administration
Study No.: 321411	Semaglutide: The access of semaglutide to the mouse brain following peripheral administration

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

NDA 209637, Federica Basso, 08/02/2017

4 Pharmacology

4.1 Primary Pharmacology

Semaglutide: Neuronal activation in mouse brain following semaglutide administration (Non-GLP compliant Study #: 321411)

The immediate early gene cFos, a marker of neuronal activation, is activated in the brain following peripheral semaglutide administration. To identify the areas of the brain activated following peripheral semaglutide administration and determine if semaglutide activated areas of the brain involved in appetite regulation, diet induced obese (DIO) male C57BL/6J mice were dosed with semaglutide (0.01 mg/kg, n=8) or vehicle (n=8) and euthanized four hours following administration. cFos immunoreactivity was evaluated in the whole brain by laser sheet fluorescence microscopy and quantified using an automated *segmentation methodology. Follow up on select brain regions was done by co-staining for cFos and calcitonin gene-related peptide (CGRP).*

Following subcutaneous administration of semaglutide (0.01 mg/kg), increased cFos activity was observed in several forebrain and brain stem areas known to express the GLP-1R and to modulate energy intake. In the brain stem, increased cFos activity was observed in the nucleus of the solitary tract (NTS), the dorsal motor nucleus of the vagus nerve (DMX) and in the circumventricular organs devoid of a blood brain barrier, such as the area postrema (AP), the vascular organ of the lamina terminalis (OV), and the subfornical organ (SFO). In the forebrain, increased cFos activity was observed in the central amygdala (CeA), bed nuclei of the stria terminalis (BST), parabrachial nucleus (PB), parasubthalamic nucleus (PSTN), the midline group of the dorsal thalamus (MTN), the lateral preoptic area (LPO), and the lateral hypothalamic area (LHA). In the PB, a subset of the cFos positive cells were identified as CGRP cells. These cells along with CeA, PB, MTN have previously been described as part of a neuronal circuit receiving projections from the AP and the NTS and are also associated with regulation of food intake.

Figure 1: cFos positive signal in different brain regions from C57Bl/6J mice administered once subcutaneous with 0.1 mg/kg semaglutide or vehicle

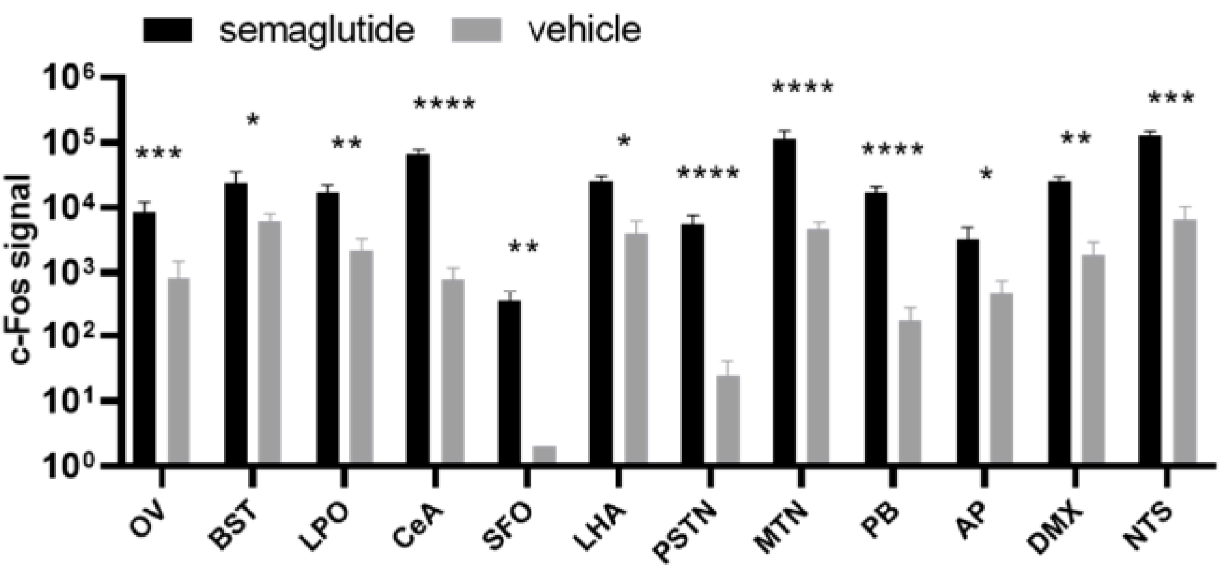


Figure copied from the Applicant's submission (Figure 2). Data are presented as means of the signal (arbitrary units) ± SEM. *p<0.05, **p<0.01, ***p<0.001, ****p<0.00001 semaglutide versus vehicle. OV: Vascular organ of the lamina terminalis, BST: Bed nuclei of the stria terminalis, LPO: Lateral preoptic area, CeA: Central amygdala nucleus, SFO: Subfornical organ, LHA: Lateral hypothalamic area, PSTN: Parasubthalamic nucleus, MTN: Midline group of the dorsal thalamus, PB: Parabrachial nucleus, AP: Area postrema, DMX: Dorsal motor nucleus of the vagus nerve, NTS: Nucleus of the solitary tract.

Semaglutide: The access of semaglutide to the mouse brain following peripheral administration (Non-GLP compliant Study #: 321411)

To study the that areas of the brain that are targeted by semaglutide after subcutaneous administration, male C57BL/6J mice were subcutaneously given 0 (vehicle PBS) for 5 days or 0.04 (Day 1), 0.07 (Day 2), and 0.15 mg/kg semaglutide-VT750 or fluorescently labeled semaglutide (Days 3-5) daily. Six hours after *the last dose, the mice were euthanized, and the brains were collected for imaging by laser sheet fluorescence microscopy.*

After repeated, subcutaneous administration, fluorescently tagged semaglutide (semaglutide-VT750) was predicted to reach steady state plasma levels. Semaglutide-VT750 was detected in circumventricular organs (area postrema and median eminence) that are not protected by the blood brain barrier and express GLP-1Rs. Semaglutide-VT750 was also detected in sections of the brain that are protected by the blood brain barrier including the hypothalamus (including the arcuate hypothalamic nucleus), brain stem (including the nucleus of the solitary tract), and septum (including the caudal part of the lateral septal nucleus, triangular nucleus of septum, and the septofimbrial nucleus). These protected areas of the brain have been shown to play an important role in regulation of food uptake and body weight regulation. Similar to liraglutide (another peripherally dosed long-acting GLP-1R agonist), semaglutide does not broadly cross the blood-brain barrier and uptake appears to be driven by specialized regions of the brain such as circumventricular organs that may work through select regions close to the ventricles (such as the lateral septal nucleus and arcuate nucleus). In the arcuate nucleus, semaglutide also activates the proopiomelanocortin/cocaine- and amphetamine regulated transcript neurons expressing the GLP-1R (Knudsen and Lau 2019, Gabery, Salinas et al. 2020). A strong fluorescent signal was also observed in the meninges and choroid plexus that do not express GLP-1, which is consistent with findings from the Quantitative Whole-Body Autoradiography studies. The signal in the choroid plexus was included in the quantitative analysis as a reference.

Figure 2: Steady-state distribution of semaglutide-VT750 in mouse brain

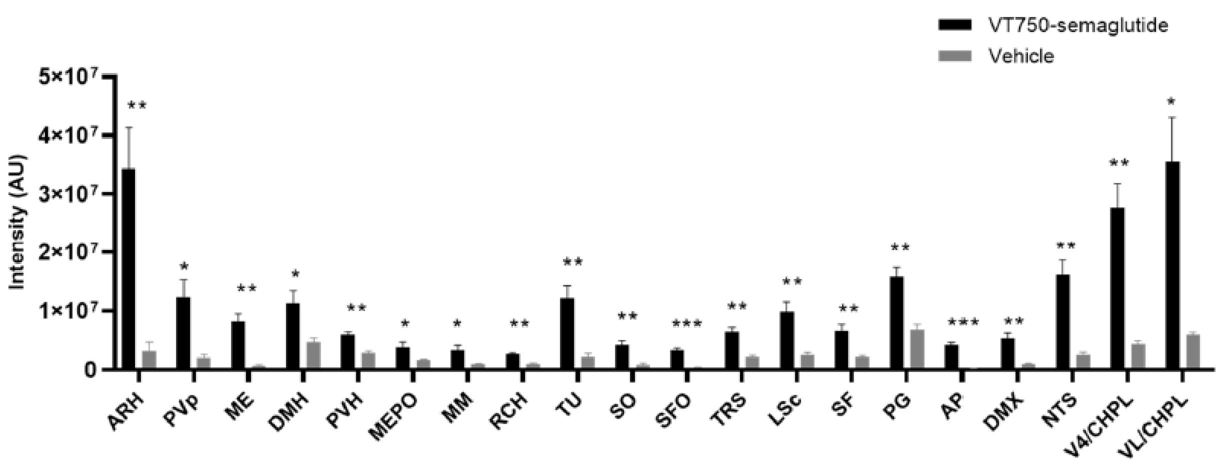


Figure copied from the Applicant's submission (Figure 2). Each bar shows the average intensity (arbitrary units) and standard error of mean (SEM) of total fluorescence signal in all brain regions that showed 2-fold enrichment and were significant when comparing semaglutide-VT750 and vehicle. *p<0.05, **p<0.01, ***p<0.001, ****p<0.00001 semaglutide-VT750 versus vehicle. ARH: Arcuate hypothalamic nucleus, PVp: Arcuate nucleus, posterior part, ME: Median eminence, DMH: Dorsomedial hypothalamic nucleus, PVH: Paraventricular nucleus of the hypothalamus, MEPO: Median preoptic nucleus, MM: Medial mammillary nucleus, RCH: Retrochiasmatic area, TU: Tuberal nucleus, SO: Supraoptic nucleus, SFO: Subfornical organ, TRS: Triangular nucleus of septum, LSc: Caudal part of the lateral septal nucleus, SF: Septofimbrial nucleus, PG: Pontine gray, AP: Area postrema, DMH: Dorsomedial hypothalamic nucleus, NTS: Nucleus of the solitary tract and VL and V4 represents CHPL in lateral and fourth ventricle respectively and are included as non-GLP-1R expressing regions.

9 Appendix/Attachments

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